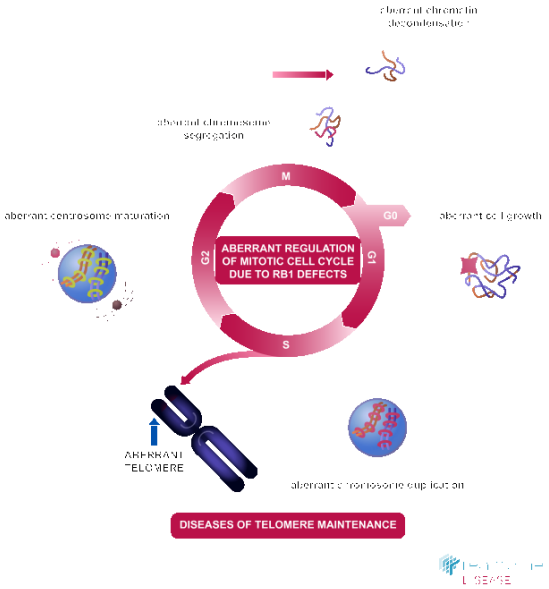
Diseases of mitotic cell cycle



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

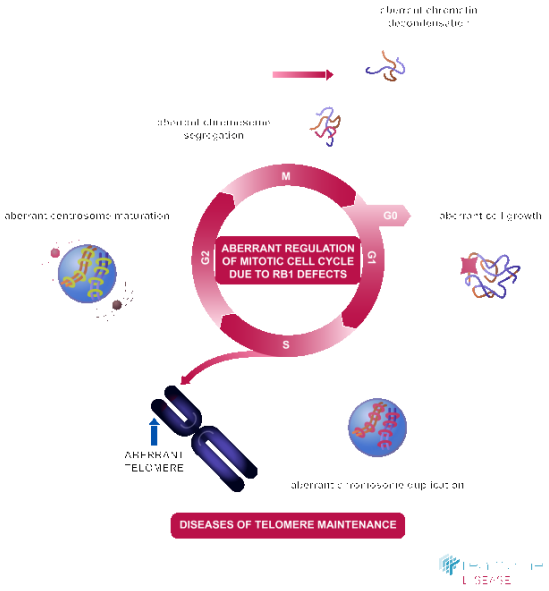
Reactome database release: 77

This document contains 3 pathways (see Table of Contents)

Diseases of mitotic cell cycle ↗

Stable identifier: R-HSA-9675126

Diseases: disease of cellular proliferation



Diseases of mitotic cell cycle are caused by mutations in cell cycle regulators (Collins and Garrett 2005, Diaz-Moralli et al. 2013), such as retinoblastoma protein RB1 (Classon and Harlow 2002), as well as proteins involved in telomere maintenance, such as ATRX and DAXX (Sarek et al. 2015). These diseases mainly include different types of cancer, hereditary syndromes such as dyskeratosis congenita that may predispose affected patients to cancer, and neurodegenerative diseases (Webber et al. 2005).

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Sarek, G., Marzec, P., Margalef, P., Boulton, SJ. (2015). Molecular basis of telomere dysfunction in human genetic diseases. *Nat. Struct. Mol. Biol., 22*, 867-74. ↗

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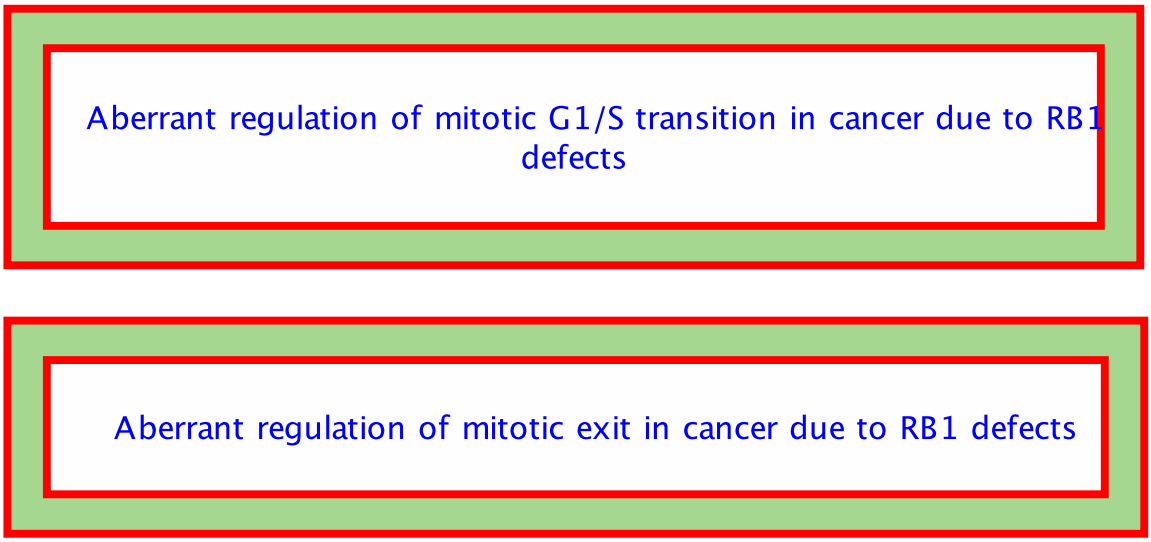
Aberrant regulation of mitotic cell cycle due to RB1 defects ↗

Location: Diseases of mitotic cell cycle

Stable identifier: R-HSA-9687139

Diseases: cancer



RB1 was the first tumor suppressor gene discovered. Bi-allelic loss of function of the RB1 gene, located at the chromosomal band 13q14, is the underlying cause of both familial and sporadic retinoblastoma, a pediatric eye cancer (reviewed by Lohmann and Gallie 2000, Knudson 2001, Corson and Gallie 2007). Besides retinoblastoma, carriers of germline RB1 mutations are predisposed to an array of other cancers, called second primary tumors, such as pinealoblastoma, osteosarcoma, leiomyosarcoma, rhabdomyosarcoma and melanoma (reviewed by Lohmann and Gallie 2000).

Inactivating somatic mutations in the RB1 gene are frequent in bladder cancer (Cancer Genome Atlas Research Network 2014), osteosarcoma (Ren and Gu 2017), ovarian cancer (Liu et al. 1994, Kuo et al. 2009, Cancer Genome Atlas Research Network 2011), small-cell lung carcinoma (reviewed by Gazdar et al. 2017), liver cancer (Ahn et al. 2014, Bayard et al. 2018) and esophageal cancer (Gao et al. 2014, Kishino et al. 2016, Salem et al. 2018).

The vast majority of RB1 mutations in cancer represent complete genomic deletions or nonsense and frameshift mutations that are predicted to result in null alleles. Missense mutations are rare and usually result in partially active RB1 mutants. Functionally characterized RB1 missense mutations and inframe deletions mostly affect pocket domains A and B and the nuclear localization signal (NLS). RB1 missense mutations reported in cancer are, however, scattered over the entire RB1 coding sequence and the molecular consequences of the vast majority of these mutations have not been studied (reviewed by Dick 2007).

The RB1 protein product, also known as pRB or retinoblastoma protein, is a nuclear protein that plays a major role in the regulation of the G1/S transition during mitotic cell cycle in multicellular eukaryotes. RB1 performs this function by binding to activating E2Fs (E2F1, E2F2 and E2F3), and preventing transcriptional activation of E2F1/2/3 target genes, which include a number of genes involved in DNA syn-

thesis (reviewed by Classon and Harlow 2002, Dick 2007). RB1 also regulates mitotic exit by acting on SKP2, a component of the SCF E3 ubiquitin ligase complex. RB1 facilitates degradation of SKP2 by the anaphase promoting complex/cyclosome (APC/C), thus preventing SKP2-mediated degradation of the cyclin-dependent kinase inhibitor CDKN1B (p27Kip1). RB1-dependent accumulation of p27Kip1 plays an important role in mitotic exit and RB1-mediated tumor suppression (reviewed by Dyson 2016).

In addition to its role in regulation of the G1/S transition and mitotic exit, RB1 also performs other, non-canonical, functions, such as its role in the maintenance of genomic stability, which is linked to its role in chromosome condensation during mitotic prophase. The impact of RB1 mutations on these E2F-independent functions, which are still important for RB1-mediated tumor suppression, has been poorly studied (reviewed by Chau and Wang 2003, Burkhart and Sage 2008, Manning and Dyson 2012, Dyson 2016, Dick et al. 2018).

Literature references

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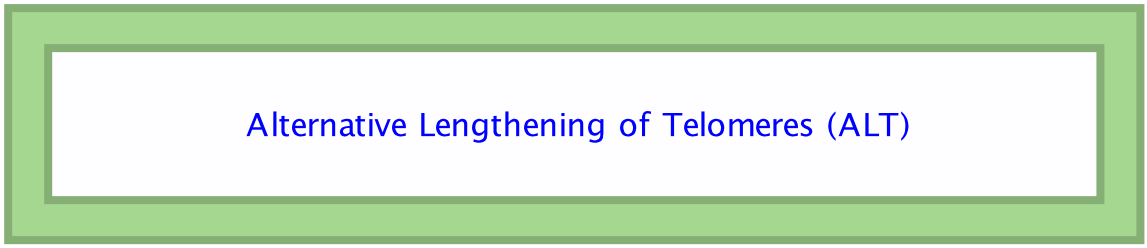
Diseases of Telomere Maintenance ↗

Location: Diseases of mitotic cell cycle

Stable identifier: R-HSA-9673013

Diseases: genetic disease



Somatic mutations or rearrangements in genes involved in telomere maintenance enable immortalization of cancer cells either through upregulation of telomerase activity or through activation of alternative lengthening of telomeres (ALT) (Killela et al. 2013, reviewed by Gocha et al. 2013, Pickett and Reddel 2015, Amorim et al. 2016, Yuan et al. 2019). Germline mutations in telomere maintenance genes lead to telomere syndromes, such as dyskeratosis congenita (DC) and Hoyeraal-Hreidarsson (HH) syndrome, characterized by impaired ability to maintain telomere lengths during growth and development, leading to abnormally short telomere lengths and genomic instability that affects multiple organs and is associated with increased risk of certain cancers (reviewed by Sarek et al. 2015).

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Editions

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